

DLVR Hopes to 'Deliver' on siRNA Potential in Cancer

By Marie Powers

BioWorld Today Contributing Writer

A bevy of U.S.-based firms – notably Alnylam Pharmaceuticals Inc., of Cambridge, Mass. – together with London-based Silence Therapeutics plc and, more recently, South Korean start-up BioMolecular Therapeutics, have been striving mightily to become first to market using RNAi-based platform technology to treat cancer.

The Canadian start-up DLVR (“deliver”) Therapeutics Inc. is the latest to jump into the fray.

DLVR, a biotech spun out of the Ontario Institute for Cancer Research (OICR) in Toronto, has developed multifunctional nanoparticles that are precisely controlled in size, enabling them to shield small interfering RNA (siRNA) of interest and deliver them safely to a target cell type or tissue. The technology is nontoxic, biocompatible and biodegradable, imitating high-density lipoprotein (HDL) – thus the moniker high-density lipoprotein-mimicking peptide-phospholipid scaffold (HPPS).

“Nature has designed a very interesting molecule that is hydrophilic on the outside and lipophilic in the core – ideal for transporting certain types of molecules or entities,” explained Frank Gleeson, a serial entrepreneur and venture capitalist who serves as DLVR’s acting CEO. “We felt this would have great promise for delivering siRNA.”

Linking specific-targeting moieties helps to target the HPPS nanoparticles so they can direct their payload to the intended tissue or cells, Gleeson added. Particle size can be optimized for a particular application. Preclinical work suggested HPPS nanoparticles could deliver siRNA payload directly to the cytoplasm of cells, avoiding destruction in the lysosome compartment and improving the therapeutic impact.

Gleeson said the technology also offers the potential to deliver chemotherapeutic agents, shielding those agents until they reach the target, then potentially altering the therapeutic index of the active drug.

“This is a platform that has the potential to have broad utility for small molecules, siRNA and imaging applications,” Gleeson told *BioWorld Today*. “At the same time, it can be used to repurpose molecules and create product opportunities that, in themselves, would create new intellectual property

– potentially, a new approved therapeutic index – and extend the life or broaden the applicability of an existing chemotherapy.”

OICR recently provided seed funding to DLVR to enable the company to advance the platform technology, with the goal of securing Series A financing in 2012 – unless an appropriate suitor approaches the company first, Gleeson said.

The HPPS nanoparticle technology, developed in the lab of Gang Zheng, associate professor at the University of Toronto and senior scientist at the Ontario Cancer Institute, University Health Network, was described earlier this year in the March 7, 2011, issue of *Small* and the June 2011 edition of *Nanomedicine*. Zheng already has demonstrated proof of concept in animal models, showing that the nanoparticles can target a human cancer xenograft expressing a targeted receptor, but not a xenograft that lacks the receptor.

Many biotechs are toiling to overcome the biggest challenge of potential siRNA-based therapeutics: delivering a siRNA of interest to a target cell at a safe therapeutic level. The field has been hindered by large molecule size and poor cellular uptake, but breakthroughs are beginning to occur, with several compounds moving into early human trials.

Although Alnylam and Silence are generally considered the big boys on the siRNA block, others are gaining attention. Last year, Dicerna Pharmaceuticals, of Watertown, Mass., partnered with Japan’s Kyowa Hakko Kirin Co. Ltd. to discover, develop and commercialize drug delivery systems and siRNA medications using Dicerna’s Dicer Substrate Technology in a deal potentially worth more than \$1.4 billion. (See *BioWorld Today*, Jan. 5, 2010.)

Meanwhile, Cerulean Pharma Inc., of Cambridge, Mass., initiated a Phase II randomized trial for non-small-cell lung cancer using its camptothecin nanoparticle and hopes to use the technology to deliver a siRNA compound. (See *BioWorld Today*, Nov. 16, 2010, and June 13, 2011.)

Similarly, Ensysce Biosciences Inc., of Houston, is carrying on the legacy of the late Richard Smalley, the

©2011. Reprinted With Permission From BioWorld[®] Today, Atlanta, Georgia.

1996 Nobel Laureate for chemistry from Rice University in Houston, using carbon nanotubes to form stable complexes with numerous active entities, including siRNA. (See *BioWorld Today*, Sept. 21, 2010.)

And South Korean start-up BioMolecular Therapeutics Inc. has taken a different approach by reducing the number of base pairs in its siRNA compounds to create shortened siRNAs, called asymmetric shorter-duplex siRNA, or asiRNA, which the company hopes to apply both to infectious diseases and cancer. (See *BioWorld Today*, Oct. 28, 2010.)

DLVR hopes to take a slice of this siRNA action, although the company still operates virtually, with OICR acting as a sort of incubator. Although DLVR has contracted with several labs and outside experts, Gleeson splits his time as the only employee while also serving as acting CEO of TORCell Therapeutics Inc., a sister OICR start-up developing an immunotherapy approach to treat acute myeloid leukemia.

(See *BioWorld Today*, July 8, 2011.)

Achieving key development milestones over the next 12 months could propel DLVR into preclinical and clinical development. On the small molecule side, the company's clinical advisors have identified several chemotherapeutics "that we think would be ideally suited to be delivered by this technology," Gleeson said. "We could alter the therapeutic index in a way that would be attractive commercially and clinically.

"For siRNA, we've developed very clear plans to demonstrate the delivery of siRNA of interest in a targeted manner," he added. "One of the interesting features of our technology is the potential to deliver directly to the cytosol, which would avoid degradation by endocytosis. We believe the combination of these two features and other benefits of an HDL-mimetic offer a very attractive technology for partnering and, ultimately, clinical development." ■